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By

Robert H. Seashore and A. C. Ivy
Northwestern University *University of Illinois*

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The Effects of Analeptic Drugs in Relieving Fatigue[1]

Robert H. Seashore
Northwestern University

and

A. C. Ivy
University of Illinois

In 1941-42 a series of studies was made of the effects of analeptic drugs on men engaged in prolonged activity. The work was prompted by the possible value of drugs in combating sleepiness, psychomotor inefficiency, and low motivation as might result from extended military activity. The results are now published since they are applicable to industrial and other phases of daily life wherein errors of human performance are to be minimized despite fatigue and prolonged wakefulness.

Physical activity in these studies consisted of, e.g., marches, guard duty, or truck and tank driving, together with a period of 24 hours of continuous wakefulness. The object of the studies was to determine the relative advantages and disadvantages of each of three analeptic drugs for use in large-scale military activity. None of the work tasks was simulated; they were the typical working tasks of the men in as nearly normal a context as possible. Since the primary concern was with the effects of the drugs on men in this actual working environment the tests and the investigators went into the "field" for the observations. The advantage of real working tasks and conditions placed limitations on the kinds and extent of observations. Tests were semiportable and only limited testing periods could be inserted into the work cycle of the men. With laboratory conditions and unlimited testing time the studies would have been expanded to the greater scientific satisfaction of the investigators but to the possible displeasure of the volunteer subjects. Since the completion of this work new technical information has been gained (19, 20, 21). Thus the testing procedures would now perhaps be modified in some details. The general approach, however, of integrating physiological, psychological, and medical investigation seems eminently successful. Furthermore, the experimental design and the results with their interpretation have applications beyond the military setting of the experiments.

[1] These studies were conducted with the assistance of James E. Birren, A. C. Van Dusen, and Stanley C. Harris, who administered the tests and assisted in the analysis and interpretation of the data. Henry C. Coopmans was instrument-maker and Claude E. Buxton aided in the design of the studies. It is impossible to thank individually the numerous volunteer subjects whose cooperation in the arduous routines made the studies possible. There were many who assisted in the arrangements for the studies whose valuable contributions must unfortunately be given an anonymous acknowledgment.

DESIGN OF PROJECTS

An attempt was made to set up fatigue studies under actual working conditions, including the usual rest and meal periods, that would approximate military operations covering a time period longer than the usual periods of wakefulness. In all but two of the experiments the subjects were soldiers, directed by field officers who were technically familiar with the special operating conditions. Six of the experiments used groups, averaging 16 men each, which were studied intensively four or more times; two mass experiments used groups of 250 men each.

An initial period of instruction and practice was given prior to each of the first experimental sessions. This was done in order to familiarize the subjects with the tests, to advance performance on the behavioral tests beyond the stages of rapid learning, and to relieve possible apprehension concerning the experiment.

Each project was called a "Vitamin Fatigue Project" in order to disguise the nature of the experimental substances. While it was indicated that the "vitamins" might aid the subject in remaining alert and relieving fatigue during prolonged duties, it was also indicated that there might be some minor deleterious side effects. The men were told that the projects were being made in order to learn which of the "vitamins" were likely to produce either good or bad effects and the extent to which they differed in these respects.

Drugs used and method of administration. The drugs used were caffeine sodium benzoate (7.5 gr.); Benzedrine Sulfate (10 mg.); desoxyephedrine hydrochloride (5 mg.); and a placebo of milk sugar (5 gr.). Each of the drugs was administered orally, in identical capsule form; the men were unable to distinguish between them.

The experimental design of the projects provided for division into squads and subgroups. Thus such factors as drug order, testing order, daily variation, etc. could be controlled or counterbalanced in such a way that the effectiveness of the drug could be statistically determined (see Table 1). Use of placebos permitted control of the psychological effects of any capsule administered.

Testing methods and instruments. All projects included a number of indices of effects of the drugs upon performance following fatiguing assignments. Some of the projects used all, others only part of the various tests. Tests were made as follows:

A. General Physiological Condition:

1. Diastolic and systolic blood pressure, average of two measurements each.
2. Pulse rate, checked until two identical 15-second counts were obtained.
3. Maximum time of breath-holding, average of 2 trials.
4. Visual flicker-fusion test. Average of three descending trials from continuous light to appearance of flicker, with the experimental light on for as short a time as possible during the test.
5. Itemized subjective reports on condition as to wakefulness, fatigue, aches and pains, bodily discomfort, etc.

B. Measures of Speed and Precision:

1. Visual discrimination reaction time (Seashore-Starmann instrument) (18). Subject places hands on telegraph keys, in front of each of which is a small ½-watt neon bulb. Instructions are to depress the key as rapidly as possible with the hand nearest to which the light appears. An average of 80 trials was used to measure speed.
2. Arm-hand steadiness in aiming (Seashore photoelectric target register) (19). The subject is seated, with elbow slightly away from his side and fingers extended horizontally holding a lever. By means of the lever he attempts to keep a small target directly in front of a light aperture, thus

controlling the light going to a photoelectric cell. In an oscillating circuit the photoelectric cell acts as a light-controlled resistance to an electric counter. The score is in terms of the sum of the distances multiplied by the times of each deviation from the true center. Measurement was made as the average score on 6 trials of 30 seconds each.

C. Measures of Tremor and Sway

1. Arm-hand tremor and sway (Seashore instrument) (20). The subject is seated as in the preceding aiming test, but holds a small ball attached to horizontal and vertical threads. The threads operate extremely lightweight ratchet mechanisms to give, on dials, the totals of movement up, down, right, and left. Six trials of 15 seconds each with eyes open were averaged.
2. Postural sway (Seashore instrument) (20).
   a. Eyes open. Subject stands erect in a comfortable position, heels together, toes diverging at an angle of 45°. Threads from a light headgear operate lightweight ratchet mechanisms, recorded on dials, to give total sway front, back, right, and left. Two trials of 1 minute each were averaged.
   b. Eyes closed. Same procedure as with eyes open.

D. Tridimensional Coordination

1. Miniature airplane test. The airplane rotates in three planes, each controlled by a separate lever or treadle. The left-hand lever controls horizontal rotation or steering (rudder); the right-hand lever controls banking movement of the wing; a right-foot treadle controls elevation (dive or climb) movements of the nose.

   During the test the airplane executes a continuous but irregular series of movements, induced by cam mechanisms. The subject attempts to counteract these movements in such a way as to keep the airplane in level flight and pointed straight ahead. Five trials of 2 minutes each were averaged.

E. Postexperimental Effects

The day after tests of the various drugs or placebo were made, each subject was given a simple report blank to fill out. The following questions were asked:

1. Did you have any trouble falling asleep?
2. Did you sleep well?
3. How long did you sleep?
4. How did you feel when you got up?

These questions were designed as a check on the possible influence of the drugs, both in preventing normal sleep and in producing effects noticeable after awakening on the following day.

THE PROJECTS

Project I: Fatigue from All-Day Marches Followed by All-Night Guard Duty

Method. A voluntary group of 2 officers and 14 enlisted men was given initial tests of physical condition and muscular coordination (all of the experimental measures). They were then divided into two equal squads. Once a week for four weeks each squad participated in an all-day, 18–20-mile hike with 26-pound packs, followed by continuous guard duty from 6 P.M. until 3 or 4:30 A.M. Immediately thereafter the testing, which required 1½ hours, was started. Thus the subjects were on duty from the time of arising at 6 A.M. until 4:30 or 6 A.M. the following morning, approximately 24 hours of continuous wakefulness.

The tests were divided into four groups, each of which required 20 minutes. By prearranged schedule, each subject always took the series of tests in the same order. Principal details of the design of the experiment are given in Table 1.

A first capsule of either the placebo or one of the analeptic drugs (caffeine, Benzedrine, or desoxyephedrine) was given after supper at 6 P.M. and a second capsule of the same kind was given at midnight. By prearranged schedule, each subject received a different drug in each of his four weekly-interval experimental periods (see Table 1).

TABLE 1

DESIGN OF THE EXPERIMENT

Group	Subjects	Drug Order	Test Order	Weekly Assignment
1A	No. 1	1, 2, 3, 4	1, 2, 3, 4	7 A.M.–5 P.M.—hike
	" 2	2, 3, 4, 1	2, 3, 4, 1	5 P.M.–6 P.M.—cleanup, eat
	" 3	3, 4, 1, 2	3, 4, 1, 2	6 P.M.–3 A.M.—guard duty
	" 4	4, 1, 2, 3	4, 1, 2, 3	3 A.M.–4:30 A.M.—testing
1B	No. 5	1, 2, 3, 4	3, 4, 1, 2	7 A.M.–5 P.M.—hike
	" 6	2, 3, 4, 1	4, 1, 2, 3	5 P.M.–6 P.M.—cleanup, eat
	" 7	3, 4, 1, 2	1, 2, 3, 4	6 P.M.–4:30 A.M.—guard duty
	" 8	4, 1, 3, 2	2, 3, 4, 1	4:30 A.M.—6 A.M.—testing
2A	No. 9	1, 2, 3, 4	2, 3, 4, 1	7 A.M.–5 P.M.—hike
	" 10	2, 3, 4, 1	3, 4, 1, 2	5 P.M.–6 P.M.—cleanup, eat
	" 11	3, 4, 1, 2	4, 1, 2, 3	6 P.M.–3 A.M.—guard duty
	" 12	4, 1, 2, 3	1, 2, 3, 4	3 A.M.–4:30 A.M.—testing
2B	No. 13	1, 2, 3, 4	4, 1, 2, 3	7 A.M.–5 P.M.—hike
	" 14	2, 3, 4, 1	1, 2, 3, 4	5 P.M.–6 P.M.—cleanup, eat
	" 15	3, 4, 1, 2	2, 3, 4, 1	6 P.M.–4:30 A.M.—guard duty
	" 16	4, 1, 3, 2	3, 4, 1, 2	4:30 A.M.–6 A.M.—testing

Because the drugs ordinarily have a latent time of approximately 30–45 minutes and an effective period of about 7–8 hours, it was expected that the men who were tested at 3 A.M. would show maximal effects of the second dose, while those who were tested at 4:30 A.M. would show the later stages of effects of the drugs.

Subjective results. As will be noted in the summary of subjective reports given for each drug (Table 2), the subject's own reports were better for all three of

TABLE 2

COMPARISON OF SUBJECTIVE REPORTS FOR EACH DRUG

Item	Measure	Placebo	Caffeine	Benzedrine	Desoxy-ephedrine
Hours sleep night before experiment	Average	7.0	7.0	6.8	7.1
	Median	7	7	7	7
Estimated number of hours subject could have continued guard duty	Average	1.9	4.2	4.2	2.8
	Median	1	2	4	2
"Capsule helped" (no. subjects)		6	12	14	12
"Capsule no effect" (no. subjects)		7	2	0	3
"Capsule hindered" (no. subjects)		2	0	0	0
Legs: Tired		2	2	6	6
Sore-aching		3	4	3	8
Pain		4	2	0	1
	Total	9	8	9	15
Feet: Tired		1	1	1	2
Sore-aching		3	1	1	6
Pain		8	6	3	3
	Total	12	8	5	11
General condition of subject: Good		5	11	14	13
Poor		10	3	0	2

TABLE 3

Comparison of Negative Subjective Symptoms for Each Drug

Symptom	Placebo	Caffeine	Benzedrine	Desoxy-ephedrine
Excessive sleepiness	12	5	3	9
Visual or auditory impairment	9	6	5	9
Vertigo	4	2	2	3
Easily fatigued	9	2	1	6
Feeling of heat and sweating	2	0	4	6
Tremors	7	9	6	11
Impaired coordinations	7	4	2	8
Palpitations or cardiac distress	3	2	2	1
Stuttering or blocking of speech	1	1	1	4
Difficulty in concentrating	5	1	1	2
Slowness in reasoning	5	1	1	4
Greater effort to carry out tasks	12	1	0	8
Mentally lazy	9	1	0	2
Depressed and grouchy	7	1	0	4
Nervous, inward tension	6	2	0	4
Fidgety or restless	7	3	2	4
Indifferent and exhausted	8	2	0	5
Total	113	43	30	90

the stimulant drugs than for the placebo; Benzedrine was given a clear preponderance of favorable reports over each of the other stimulant drugs.

In this connection, it was of interest to note that the subjects could tell rather accurately when they had been given a control dose of "dud," as they described it. The experimenters, too, were able to recognize fairly accurately when the subjects had received the placebo, merely by sleepy behavior exhibited during the test period. They were also often able, by the more buoyant attitude and behavior exhibited, to distinguish subjects receiving Benzedrine from those receiving the other two stimulants.

Negative subjective symptoms, summarized in Table 3, showed that the drugs differed significantly among themselves, with Benzedrine ranking first in freedom from negative symptoms, followed closely by caffeine and markedly separated from desoxyephedrine, which in turn differed only moderately from the placebo.

Positive subjective symptoms, summarized in Table 4, showed Benzedrine to be first in desirable effects, followed by caffeine, desoxyephedrine, and the placebo.

Objective results. Results from the administration of objective physiological and behavioral measurements are summarized in Table 5. The probabilities, p, in Table 5 were derived from the t test of significance for matched samples (4). The p values indicate the percentage of future cases in which such a difference between means would likely occur by

TABLE 4

Comparison of Positive Subjective Symptoms for Each Drug

Symptom	Placebo	Caffeine	Benzedrine	Desoxyephedrine
No sleepiness	3	9	11	6
Talkative and excited	1	7	10	5
Feeling of exhilaration	1	5	10	4
Total	5	21	31	15

TABLE 5

PERCENTAGE OF ABSOLUTE DIFFERENCES BETWEEN MEAN RAW SCORE UNDER PLACEBO AND EACH DRUG CONDITION, WITH *p* INDICES FOR STATISTICAL SIGNIFICANCE OF DIFFERENCE OF RAW AND *z* SCORES*

Measure or Test	Caffeine vs. Placebo			Benzedrine vs. Placebo			Desoxyephedrine vs. Placebo		
	% abso. dif. in av. raw scores	*p* indices: Raw score	*p* indices: *z*-score	% abso. dif. in av. raw scores	*p* indices: Raw score	*p* indices: *z*-score	% abso. dif. in av. raw scores	*p* indices: Raw score	*p* indices: *z*-score
Pulse	2	50–60	20–30	17	*1*	*1*	9	5–10	*1–2*
Systolic blood pressure	3	5–10	30	5	*2–5*	*2–5*	3	10–20	20–30
Diastolic blood pressure	7	*2–5*	*1–2*	8	*1*	*1–2*	4	10–20	10–20
Pulse pressure	4	10–20	30–40	0	90–100	80–90	1	80–90	60
Breath-holding	8	20–30	10–20	9	20–30	10–20	10	*2–5*	*1*
Flicker-fusion	5	10–20	30–40	7	*1*	*2–5*	3	10–20	50–60
Discriminatory reaction time	5	10–20	10–20	6	*1*	5–10	6	*1*	*2–5*
Steadiness in aiming	8	30–40	5–10	6	50–60	10–20	7	30–40	10–20
Tridimensional coordination (all)	15	10–20	*2–5*	31	*1*	*1*	22	*2–5*	*1*
Tridimensional coordination (4+5)/2	22	5–10	*2–5*	42	*1*	*1*	26	*1*	*1*
Hand-arm sway	5	60–70	80–90	20	*2–5*	5–10	18	*2–5*	5–10
Body sway, eyes closed	0	90–100	80–90	5	60–70	40–50	11	20–30	50–60
Body sway, eyes open	3	60–70	40–50	12	5–10	*1–2*	11	*2–5*	*1–2*
Medians	5	10–20	20–30	8	*2–5*	*2–5*	9	*2–5*	*1–2*

* Statistically significant values, i.e., $p < .05$ are in italics.

chance alone.

Two such indices are given for each drug, as compared with the placebo: (*a*) comparison of average raw score of all subjects at the time of taking the particular drug, without regard to the week of the experiment, and (*b*) in terms of *z* scores, or the standard deviations above or below the mean, of all persons taking the test during the week for which each comparison was made. This second index corrects for the fact that some of the tests showed significant continued effects of practice. Where such practice effects were fairly large, the second index usually shows greater significance, but where little improvement resulted from practice, the statistical treatment sometimes showed slight reversals of significance (probably attributable to the small number of subjects studied).

In examining Table 5, it will be seen that all the behavioral tests showed indices favoring use of the three stimulants, ranging from moderate to high degrees of statistical significance. Breath-holding, a measure of motivation and, to some degree, of specialized strength, showed a moderate improvement for all three stimulants.

Visual flicker-fusion, often considered to be primarily an indicator of neural fatigue or recovery, showed smaller but consistent improvement for Benzedrine, lesser improvements for the other two stimulants. Speed of visual discriminative reaction time was slightly but reliably improved by all three stimulants. Hand-arm sway was markedly improved for Benzedrine and desoxyephedrine, slightly improved for caffeine. To a lesser extent the same was true for postural sway with eyes open.

Postexperimental results. A summary of results is shown in Table 6. The average number of hours of sleep

TABLE 6

SUBJECTIVE REPORTS ON SLEEP AND CONDITION FOLLOWING EXPERIMENT*

Subjective Report	Placebo	Caffeine	Benzedrine	Desoxy-ephedrine
Average no. of hours sleep	4.7	4.5	4.0	4.8
Median no. of hours sleep	4.5	4	4	5
Trouble falling asleep (no. of subj.)	0	4	3	[illegible]
Good restful sleep (no. of subj.)	13	10	11	12
Good condition after sleep (no. of subj.)	10	8	10	7
Poor condition after sleep (no. of subj.)	4	5	4	7

* Benzedrine was the only drug for which there was a report from every subject.

(slightly over four) following the experiment was surprisingly short. This was attributed to the fact that the subjects were accustomed to late night hours and early rising, and to the noisy daytime conditions in the barracks.

No significant difference was found among the stimulants or the placebo with respect to average length of sleep following the experiment. The stimulants did not differ significantly from one another, or from the placebo, in quality of sleep or as to general condition after sleep.

Summary of results. Of the three stimulants, in general the best (subjective, objective, and postexperimental) results were obtained with Benzedrine. Caffeine produced desirable subjective reports with but little improvement in motor performance. Desoxyephedrine produced little change in subjective reports but produced improvements in motor effects that were as good as, or slightly better than, those with Benzedrine.

PROJECT II: BATTALION MARCH EXPERIMENT

Method. Four batteries of soldiers of about 70 men each participated in two regular training marches of 10–12 miles each on successive afternoons. The marches were largely on paved roads, over slightly rolling country, with a little cross-country work and in warm, humid weather. Equipment carried weighed approximately 26 pounds.

The three stimulants and a placebo, as used in Project I, were administered to two different batteries of men as follows:

Battery	First March No.	Second March No.
E	1—placebo	3—Benzedrine
F	2—caffeine	4—desoxyephedrine
G	3—Benzedrine	1—placebo
H	4—desoxyephedrine	2—caffeine

At the end of each march each man filled out individual cards which reported subjective effects. The more extended battery of sensorimotor tests was not used in this study. The number of men reporting for each drug was as follows: placebo, 131; caffeine, 148; Benzedrine, 137; desoxyephedrine, 147.

Subjective results. Since each drug was administered to approximately equal numbers of subjects on both marches, variation between marches was counterbalanced and should not affect interpretation.

Ranking the drugs according to favorable effect on the subjects, as indicated by responses on the questionnaire card, yielded the following results:

	Drug Order
Least difficulty with march	3, 4, 2, 1.
Least foot trouble	3, 4, 2, 1.
Least leg trouble	4, 3, 1, 2.
Least general fatigue	3, 1, 2, 4.
Greater "help" from capsule	4, 3, 2, 1.

Assigning equal weights to each of the

above items, the over-all order of merit among the drugs would be 3 (Benzedrine), 4 (desoxyephedrine), 2 (caffeine), and 1 (placebo). This finding agrees with those of Project I, which showed Benzedrine to produce the best subjective effects, but reverses the order between caffeine and desoxyephedrine.

Summary of results. Both Benzedrine and desoxyephedrine appeared to produce effects which were large enough to be recognized by untrained soldiers during a march. None of the stimulants showed any greater percentage of ill effects than did the placebo. The fact that at least 15 per cent of the subjects taking the placebo reported beneficial effects indicates the significance of suggestion in this as in many other medical treatments.

Project III: Commercial Truck Drivers Experiment

Method. Drivers of large semi-trailer trucks, following their usual runs, were used for the experiment. Most of their work, including loading boxes of groceries, driving, and unloading, was done at night and alone. The total number of working hours ranged from 6 to 15 hours, with brief opportunities for time out for meals. Each driver was tested following one of his normal cross-country trips.

Before each trip an envelope containing one of the three stimulants or the placebo, as used in previous experiments, was issued to the driver with written instructions concerning the time (5–6 hours prior to end of run) to take the capsule. In every case the driver signed a slip giving the time he took the capsule.

Results. Relative shortness of most of the routes and inability to maintain fixed schedules because of mechanical and other difficulties prevented fixed intervals between drug ingestion and testing and precluded a detailed analysis of findings. This experiment did establish that a considerably longer (6–15 hours) and more fatiguing schedule would be required before effects of the drugs could be properly evaluated on truck drivers.

In general, while subjective effects of the stimulants were desirable and no important undesirable side effects were produced, there would probably be relatively slight benefits from routine use of the drugs by drivers on ordinary short schedules.

Project IV: Army Truck Drivers Experiment

Method. Two groups, each consisting of an officer and eight drivers, worked on alternate days driving 2½-ton heavy-duty army trucks from 7 A.M. to 12 noon, from 1 to 5 P.M., from 6 P.M. to midnight, and, after a light lunch, from 12:15 to either 3 or 4:30 A.M. A first capsule of either caffeine, Benzedrine, desoxyephedrine, or the placebo was given after supper at 6 P.M. and a second capsule of the same kind was administered directly after the midnight lunch. Drives were made under a variety of conditions, including three hours of "blackout" on very poor country roads.

Immediately following completion of the drives, essentially the same subjective, physiological, and sensorimotor behavioral tests as used in Project I were made.

Subjective results. There were relatively few negative subjective symptoms associated with any of the stimulants and no significant differences between them. Among the positive subjective findings, Benzedrine was reported as eliminating sleepiness in over 50 per cent; caffeine had a slight effect in a few subjects. All three of the stimulants exceeded the placebo in respect to the estimate of

additional time subjects thought they could continue the same work.

Objective results. Physiological measurements were statistically significant in only two instances: Benzedrine produced an average increase of 18 per cent in the pulse rate and desoxyephedrine produced a 12 per cent increase. Since the normal pulse rate for these subjects was lower than that of the general population, these increases are not viewed as serious. Also, none of the other studies with Benzedrine produced such a pulse rate increase.

Flicker-fusion produced small but statistically significant improvement and the photoelectric aiming test produced a slightly greater degree of improvement with all three stimulants. Reaction time showed small and moderately significant differences in favor of Benzedrine and desoxyephedrine. Hand-arm sway and postural sway with eyes open showed only moderately significant differences in favor of all three stimulants; postural sway with eyes closed showed larger and more significant differences for all three.

Postexperimental results. Only two subjects, one of whom had desoxyephedrine, the other caffeine, had any difficulty in falling asleep. The only subject reporting feeling bad on awakening had received a placebo.

Summary of results. This experiment produced less observable or measurable degrees of fatigue and therefore fewer possible advantages attributable to the stimulants. What advantages did appear, however, were in line with the findings on the subjects in Project I.

Project V: Tank Drivers Experiment

Method. Four tank crews, each consisting of four men, worked for five-hour periods on five successive days. Each man served as driver for 2½ hours, in rotation, thus driving only every other day. Since previous experiments seemed to indicate that in general Benzedrine was the drug of choice among the three stimulants, this experiment was limited to a comparison of Benzedrine with the placebo. Each member of a crew received the same drug, the capsule being administered just prior to the five-hour drive. Crews were tested immediately upon completion of the runs.

Subjective results. The only negative subjective symptom of even approximately statistical significance was the greater number of mild headaches and complaints about excessive dust under placebo conditions. Among the positive subjective effects Benzedrine showed only moderate advantages in avoiding sleepiness during the experiment and in reducing complaints about muscular conditions.

Objective results. All the sensorimotor tests showed relatively slight absolute improvements under Benzedrine, with moderately significant improvements in reaction time, photoelectric aiming, and postural sway with eyes closed.

Summary of results. Considering the short work periods employed, the most significant findings in this experiment were that administration of the drug under the extreme heat, vibration, and other aspects of tank operation did not produce undesirable side-effects and that use of Benzedrine did produce moderately desirable effects.

Project VI: Effects of Hot-Moist and Hot-Dry Temperatures upon Physiological and Psychological Functions

At the time these experiments were made there was a current belief that Benzedrine might inhibit perspiration. Since it was anticipated that use of the drug might be used under desert and tropical

conditions, it was important to find out if normal body-cooling mechanisms would be inhibited by use of the drug under hot-dry or hot-moist conditions.

Method. Eight students (six from medical schools) in groups of four each served as paid subjects. On six successive days sensorimotor performances were measured prior to and following exposure to high temperature conditions. No physical work was done. Each group was given the preliminary series of tests late in the morning, followed by a light lunch and administration of either a Benzedrine or a placebo capsule. They were then placed in one of the controlled temperature rooms for a period of six hours.

In the hot-moist room, the average temperature was 86° F. dry bulb and 85° F. wet bulb, with a relative humidity so high that the air was usually foggy. In the hot-dry room, the average temperature was 117° F. dry bulb, 85° F. wet bulb, with a relative humidity of approximately 17 per cent. During the six hours spent in the controlled temperature rooms, the previously trained medical students in the group took rectal temperatures and pulse and blood pressure readings on all subjects at intervals of approximately 40 minutes.

Summary of results. Six hours of exposure to hot-moist and to hot-dry conditions did not produce evidence of undesirable effects from either Benzedrine or the placebo. Operation of the body-cooling mechanism was adequate under both, as shown by visible evidence of perspiration under hot-moist conditions, by a very heavy water and salt intake under hot-dry conditions, and by absence of any unusual changes in rectal temperature, pulse rate, or blood pressure. The slight differences shown in sensorimotor measurements were, in nearly all cases, in favor of the use of Benzedrine.

Project VII: Desert Infantry March Experiment

Method. Since night marches are the typical operation under desert warfare conditions, marches were started at either 7 or 8 P.M. Two officers and 16 enlisted men participated in each of four experiments. The first two experiments consisted of 7 P.M. to 6 A.M. marches of 17–22 miles, with 8-pound packs, followed by guard duty until either 10 or 11 A.M. When these experiments did not prove to be sufficiently fatiguing, the guard duty was changed to additional marching (making a total of about 26–28 miles) for the second two experiments.

For the first two experiments only one capsule of either Benzedrine or the placebo was administered directly after the midnight lunch at 12:30 A.M. On the third and fourth marches, a second capsule of the same kind was administered at 6 A.M., just prior to breakfast. Subjects reported for the test program at either 10 or 11 A.M.

Subjective and postexperimental results. No statistically significant differences between Benzedrine and the placebo were shown for either negative or positive subjective symptoms or for records of sleep following the experimental periods. Of the few complaints of tired muscles, much smaller percentages were reported following Benzedrine administration.

Objective results. Of the physiological measures of circulatory conditions, Benzedrine gave the greatest score in each case, although absolute changes were quite small. The best score on each of the behavioral tests was in favor of Benzedrine, although only in body sway with eyes opened and closed and in flicker-fusion were improvements of statistical significance.

Summary of results. In general, there

appeared a tendency toward improvement in performance under the Benzedrine condition, even though absolute changes in many instances did not reach statistical significance for either the subjective reports or objective tests. Positive influence of the Benzedrine was more apparent under the third and fourth experiments which were more fatiguing than were the first two.

Project VIII: Desert Tank Experiment

Method. Four groups of four men each served on alternate days for one pretesting period and four experimental sessions. The first two experiments used six hours of driving time, the third and fourth experiments used seven hours of driving time. Tests were made after completion of the drives. One capsule of either Benzedrine or the placebo was administered 4½–5 hours before testing.

Subjective and postexperimental results. There were no significant differences between Benzedrine and the placebo for either negative or positive subjective symptoms. Only two negative reports on sleep following the experiment were obtained, each of which was under the placebo condition.

Objective results. Absolute changes in circulatory condition were of no practical significance. Although better scores were made under the Benzedrine condition in all but one (discriminative reaction time) of the objective tests, absolute differences were so small as to be of no statistical significance.

DISCUSSION

Since too little is known about the fundamental nature of fatigue and recovery, it is impossible to interpret in detail the present findings. Results of behavioral studies such as the present will, of course, eventually need to be traced back to their detailed physiological and biochemical bases. Since these studies were conducted, new evidence is available about the effects of stimulants on the human subjects (1, 2, 3, 5, 6, 8, 9, 10, 11, 24, 25). They point, as did the present work, to the subtle nature of fatigue and to the necessity for having the subjects perform for periods much longer than conventionally regarded as fatiguing before drug effects may be demonstrated reliably.

The physiological effects of fatigue may be such that larger absolute values or larger relative differences in stimuli become necessary in order to produce the same effectiveness of response. The stimulant drugs used in these experiments were observed to overcome boredom and to produce a more alert attitude in the subjects. This may have resulted from an influence on the background stimulation. Use of stimulants may improve the performance of a task by facilitating the direction of attention to stimuli related to the main task. Thus the subject may discover new leads to effective action such as short cuts, or detect incipient errors which might lead to danger if uncorrected.

In evaluating the preceding experimental results, certain implications of the method employed should be recognized. Since we usually compared end results following use of a stimulant with those following use of a placebo, the differences measured represent only a part of the total fatigue, the remainder being effective under both stimulant and placebo conditions. Thus our measurements of differences in fatigue are conservative indices. Also, since we studied,

primarily, differences between, and results of, stimulant and placebo conditions, we did not measure psychological benefits of drug administration since they were also present in the placebo.

Deleterious side effects or aftereffects of the stimulants were notably absent. It is probable that this was due in part to the moderate dosages used. It is also possible that heavy work, such as was performed, resulted in rapid, complete metabolism of the drugs. Considering evidence from the experiments with the battalion of men on training marches and the more intensive studies made with groups of about 16 men each, it seems reasonable to anticipate no greater ill effects from these drugs than would be expected by chance from other mild medical treatments—so few, in fact, as to be negligible.

With the possible exception of the first experiment, only relatively slight degrees of fatigue were observed or measured during the entire project. It was gratifying to learn that the men were in sufficiently good condition to carry out the experiments—which civilians and officers alike had estimated as near the limit of capacity—with such relatively slight decrement in well-being and efficiency. However, since, in general, the most significant benefits from use of the stimulants appeared in those experiments where observable fatigue was greatest, a more clear-cut demonstration of statistical significance would probably have resulted from use of subjects exhibiting greater degrees of fatigue.

Previous laboratory experiments with Benzedrine showed relatively little effect on sensorimotor coordinations when only slight fatigue was involved (4). This series of experiments, also, demonstrated limitation of benefit from stimulants under conditions of only slight fatigue. Therefore it would seem to follow that, except under certain conditions, stimulants should be administered only when fatigue is greater than that resulting from normal work. Exceptions would include such conditions as standing guard or driving at night, where alertness is important. In this connection, it should be recognized that, in the vast majority of comparisons made between the stimulants and the placebo in this study, differences were consistently in favor of the stimulants.

Medical Comment and an Opinion

If tired troops, who must serve regardless of fatigue, cannot get coffee, a stimulant is indicated. Benzedrine will keep them awake and alert as does coffee but, unlike the occasional effect of coffee, will not make their muscular action unsteady and jerky. Since it is not metabolized as rapidly as caffeine, the effect of Benzedrine should last longer.

We have seen no deleterious effects or objectionable side-reactions in 75 male medical students given 10 mg. of Benzedrine orally. Most reported that, 6–8 hours after taking the dose, they fell asleep readily after going to bed. In the physically fatigued soldiers used in these experiments, no significant disturbance of sleep was observed and no deleterious effects from Benzedrine were noted.

Benzedrine is not a substitute for sleep and rest; it should be used for emergencies only and its distribution should be kept under supervision.

In tired men or in men doing physical work, 10 mg. Benzedrine every six hours for two or three doses is not excessive. In light work, 5 mg. as a first dose, to be repeated in one or two hours, is perhaps preferable, although we have not given the 10 mg. in such divided doses. The 5-mg. dosage would be less likely to harm the very occasional subject with idiosyncrasy.

SUMMARY

A series of experiments was made by Northwestern University investigators for the Committee on Medical Research of the Office of Scientific Research and Development. Eight projects were used to study the effects of currently used stimulant drugs in promoting wakefulness and improved motivation, as well as their effects in overcoming fatigue during prolonged activity.

The drugs, administered orally in identical capsule form, were: caffeine sodium benzoate (7.5 gr.) Benzedrine Sulfate (10 mg.); desoxyephedrine hydrochloride (5 mg.); and a placebo of milk sugar (5 gr.). The drugs were always called "vitamins" and the projects "Vitamin Fatigue Projects" so that the nature of the experimental material was unknown to the subjects.

Records and tests included the following:

1. General physiological condition: systolic and diastolic blood pressure; pulse rate; breath-holding; visual flicker test; itemized subjective report.

2. Measures of speed and precision: visual discriminative reaction time; arm-hand steadiness.

3. Measures of tremor and sway; postural sway with eyes open and closed.

4. Tridimensional coordination.

5. Postexperimental subjective reports.

In the eight experimental projects, six groups, averaging about 16 subjects each, were used, and in one project four groups of about 70 subjects each were used. In the first four projects effects of all three of the stimulants were compared with the placebo. Because Benzedrine appeared to give superior results, only this drug was used for comparison with the placebo in the last four projects.

Project I produced degrees of fatigue that were more observable and measurable than those of the other seven projects. Project I is reported in detail, the other projects are merely summarized. A summary of significant results of subjective reports and objective tests is given in the appendices.

In general it may be stated that comparison of results, after using each of the three stimulants, with those after using the placebo, showed the following:

Caffeine: desirable subjective effects; negligible improvements in sensorimotor coordinations.

Desoxyephedrine: insignificant subjective improvements; significant improvements on sensorimotor measurements.

Benzedrine: subjective effects as good as those of caffeine; sensorimotor improvements nearly as great as those with desoxyephedrine.

None of the stimulants showed more than relatively unimportant side-effects.

APPENDIX 1-A

Number of Subjective Reports under Placebo and Benzedrine

Subjective Report	Project I March & Guard		Project IV Truck Drivers		Project V Tank Crews		Project VII Marches		Project VIII Tank Crews	
	Plac.	Benz.	Plac.	Benz.	Plac.	Benz.	Plac.	Benz.	Plac.	Benz.
Positive symptoms	2	31	1	4	4	8	6	9	5	3
Negative symptoms	113	30	27	23	124	102	36	41	20	13
Tired muscles	12	5			11	3	12	7	0	2
Headache:										
Yes			0	2	6	1	3	3	1	1
No			16	14	33	38	32	33	29	31
Capsule:										
Helped	6	14	11	13	10	12	21	27	18	25
Hindered	7	0	2	2	2	0	0	0	0	0
No effect	2	0	3	3	26	27	12	8	12	6

APPENDIX 1-B

Number of Subjective Reports under Placebo and under Caffeine and Desoxyephedrine

Subjective Report	Project I March and Guard			Project IV Truck Drivers		
	Placebo	Caffeine	Desoxy-ephedrine	Placebo	Caffeine	Desoxy-ephedrine
Positive symptoms	2	12	9	1	5	5
Negative symptoms	113	43	90	27	25	25
Tired muscles	12	8	11	5	5	5
Capsule:						
Helped	6	12	12	11	13	15
Hindered	7	2	3	2	0	0
No effect	2	0	0	3	2	1

APPENDIX 2-A

Percentage of Absolute Difference in Objective Test Scores under Placebo and Benzedrine Conditions

Measure or Test	Project I March and Guard	Project IV Truck Drivers	Project V Tank Crews	Project VI		Project VII Marches	Project VIII Tank Crews
				Dry-Hot Temp.	Wet-Hot Temp.		
Pulse rate	17*	18*	5	12	2	6	8*
Systolic blood pressure	5*	4	2	2	2	3*	2
Diastolic blood pressure	8*	5	5*	3*	4	4*	2
Pulse pressure	0	0	4	3	0	3	4
Breath-holding	9	14	2	6	9		
Flicker-fusion	7*	3*	1	15	1	2*	1
Discriminative reaction time	6*	5	3	3	4	1	4
Photoelectric aiming	6	8	5*	4	10*	2	2
Tridimensional pursuit†	31*	2	15				
Hand-arm sway	20*	20*					
Postural sway:							
1. Eyes closed	5	26*	14*	12*	9*	7	1
2. Eyes open	12	14	1	8*	8	8*	3
Serial discrimeter						1	6
Median	7.5*	8	4.5	7	8.5	3.5	4

* Statistically signifiant (p values .01–.05).
† z-score differences given here because of learning function.

APPENDIX 2-B

Percentage of Absolute Difference in Objective Test Scores under Placebo and Caffeine or Desoxyephedrine

Measure or Test	Project I March and Guard		Project IV Truck Drivers	
	Caffeine	Desoxy-ephedrine	Caffeine	Desoxy-ephedrine
Pulse rate	2	9	2	12*
Systolic blood pressure	3	3	3	5
Diastolic blood pressure	7*	4	3	2
Pulse pressure	4	1	3	5
Breath-holding	8	10*	10	6
Flicker-fusion	5	3	3*	4*
Discriminative reaction time	5	6*	1	3*
Photoelectric aiming	8	7	5	10*
Tridimensional pursuit†	15*	22*	23*	10
Hand-arm sway	5	18*	8	11
Body sway:				
1. Eyes open	0	11	19*	23*
2. Eyes closed	3	11*	13	27*
Median	5	9*	4	8

* Statistically significant (p values .01–.05).
† z-score difference given here because of learning function.

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